Fat embolism syndrome after trauma: What you need to know

Junsik Kwon, MD *and* **Raul Coimbra, MD, PhD**, *Moreno Valley, California*

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ABSTRACT: Fat embolism syndrome refers to a systemic condition caused by the circulation of fat droplets in the bloodstream, reaching various target organs typically after major bone fractures or related surgical procedures. Although most cases resolve spontaneously, severe instances can lead to significant respiratory failure, neurological damage, and even mortality. Therefore, appropriate prevention, timely diagnosis, and management are crucial for trauma patients at risk. The objective of this review article is to explore the definition, epidemiology, risk factors, clinical presentation, and pathophysiology of fat embolism syndrome. Furthermore, it aims to examine current recommendations for the accurate diagnosis, prevention, and treatment of it, providing a comprehensive guide for the effective management of patients prone to this condition. (*J Trauma Acute Care Surg.* 2024;97: 505–513. Copyright © 2024 Wolters Kluwer Health, Inc. All rights reserved.)

KEY WORDS: Fat embolism syndrome; cerebral fat embolism; respiratory insufficiency; long bone fractures; outcomes.

DEFINITION (FAT EMBOLISM VS. FAT EMBOLISM SYNDROME)

Fat embolism (FE) is defined as the circulation of fat droplets in the bloodstream reaching distant organs, which can lead to fat embolism syndrome (FES), a severe clinical presentation manifested by symptoms such as petechial rash, cognitive impairment, and respiratory distress, typically manifesting within 24 hours following an injury. Research conducted through autopsies has shown that approximately 90% of cases with skeletal trauma have microfat droplets in the pulmonary vessels.[1] Although fat embolism is a common phenomenon, most cases are asymptomatic, highlighting the need to distinguish clinically significant FES from simple fat embolism. In 1924, Gauss[2] categorized FES into three clinical types: (1) a pulmonary type characterized by symptoms of pulmonary emboli; (2) a cardiac type involving microvascular coronary embolization presenting with hypotension, dyspnea, and tachycardia; and (3) a neurologic type resulting from cerebral embolism.

EPIDEMIOLOGY

The prevalence of FES and fat embolism exhibits considerable variation across studies, influenced by the methodology used to identify patients and the etiology involved. Research also shows considerable variability based on study design. Long-term retrospective studies typically report lower incidence rates. For instance, Robert et al.[3] observed a 0.26% incidence of clinically apparent FES in a 25-year retrospective analysis of individuals diagnosed with pelvic and lower extremity fractures. Similarly, Bulger et al.[4] documented a 0.9% prevalence of FES among patients sustaining femur fractures over a decade at a level 1 trauma center. In contrast, prospective studies often report higher and more consistent incidences. Fabian et al.[5] noted an 11% incidence of FES in a cohort of 92 individuals experiencing fractures of the pelvis and long bones within a 1-year timeframe, while Kallenbach et al.[6] documented a 13% incidence of FES in a study evaluating the prophylactic use of corticosteroids in fracture patients. Moreover, studies using specialized laboratory tests and postmortem examinations have identified a much higher prevalence of systemic fat emboli. Christie et al.[7] identified fat emboli in 87% of a cohort undergoing 111 invasive intramedullary procedures, using transesophageal echocardiography. Eriksson et al.[8] found pulmonary fat emboli in 82% of autopsies conducted on patients who had sustained major blunt trauma. While the systemic dispersion of fat emboli following trauma and surgical interventions is relatively common, the clinical manifestation of FES appears to be less frequent.

RISK FACTORS

Fat embolism syndrome occurs approximately four times more frequently in males and is more prevalent among young patients aged 10 to 39 years compared with older age groups. This is attributed to differences in bone marrow composition among age groups, specifically the ratios of fat and oleic acid. The inclusion of many elderly patients sustaining fractures, particularly those who often sustain low-energy isolated hip fractures, also contributes to the lower incidence of FES in clinical studies.[9] Another risk factor for FES is the sustained hypovolemic state following trauma, which disrupts the microcirculation within tissues, leading to a systemic inflammatory response and platelet activation, which facilitates the adherence of fat emboli particles from the bone marrow to the vascular wall.[10] The risk of FES is notably higher in cases involving high-energy trauma

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From the Division of Trauma Surgery, Department of Surgery (J.K.), Ajou University School of Medicine, Suwon, Korea; Division of Trauma and Acute Care Surgery (R.C.), Riverside University Health System Medical Center, Moreno Valley; Department of Surgery, Loma Linda University School of Medicine (R.C.), Loma Linda; and Comparative Effectiveness and Clinical Outcomes Research Center (J.K., R.C.), Riverside University Health System Medical Center, Moreno Valley, California.

Address for correspondence: Raul Coimbra, MD, PhD, Comparative Effectiveness and Clinical Outcomes Research Center, Riverside University Health System, 26520 Cactus Ave, CPC Bldg, Ste 102-5, Moreno Valley, CA 92555; email: r.coimbra@ruhealth.org.

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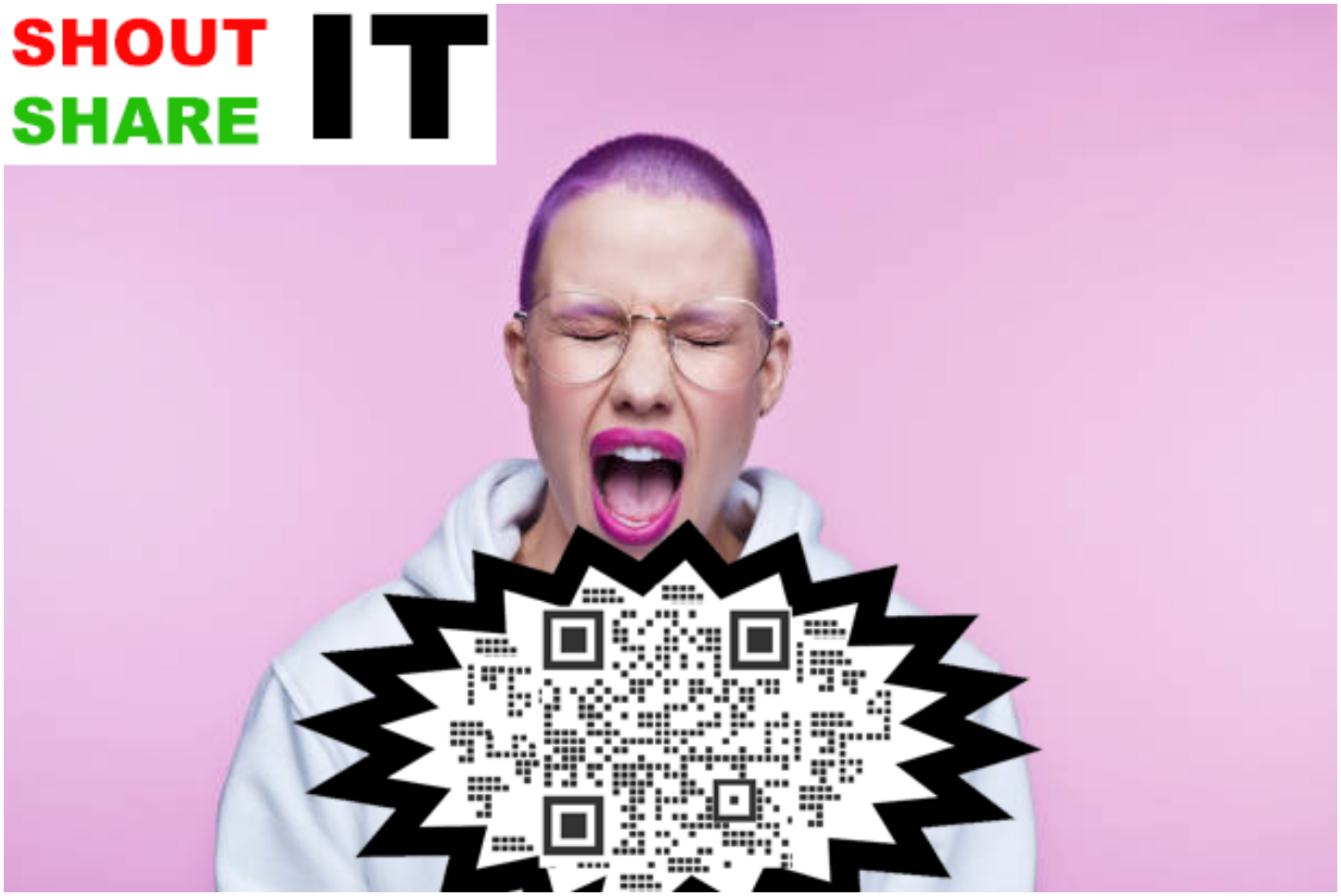
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and multiple fractures, particularly long bone fractures. Among these, fractures of the femur, excluding the femoral neck area, are most associated with FES.[9] Closed fractures demonstrate a higher propensity for precipitating FES compared with open fractures because of the increased tissue pressure at the injury site in closed fractures, which elevates the risk of fat emboli entering the systemic circulation.[11] Clinical decisions related to orthopedic operations also significantly influence the likelihood of developing FES. Delays in fracture fixation and methods of closed reduction are recognized surgical risk factors for FES.[3,4] Pape and Giannoudis[12] reported that reaming during operative fixation of long bones can disperse a greater amount of fat emboli, thereby acting as a substantial risk factor for FES. Therefore, Kröpfl et al.[13] recommended unreamed nailing after demonstrating in a baboon model that reaming increases intramedullary pressures and the subsequent extravasation of adipose tissue from the bone marrow.

CLINICAL PRESENTATION

Respiratory

The most common clinical manifestation of FES is dyspnea, with three quarters of patients diagnosed with FES exhibiting varying degrees of respiratory symptoms.[14] Dyspnea is primarily due to hypoxemia. Mild hypoxemia can occur in as many as 90% of individuals sustaining long bone fractures, even in the absence of a clinically evident FES diagnosis.[15] McCarthy et al.[16] in a prospective investigation evaluating 50 fracture patients found an increased alveolar-arterial O_2 gradient in all and a decrease in PaO_2 in 74% of them. Respiratory symptoms may initially present as subtle dyspnea; however, as the ventilation/perfusion mismatch worsens and the impairment of gas exchange deepens, conditions can escalate to respiratory failure or acute respiratory distress syndrome (ARDS), necessitating mechanical ventilatory support. Bulger et al.[4] reported that mechanical ventilation was required in 44% of patients diagnosed with FES. In a 15-year retrospective study, Arthurs et al.[17] found that 64% of patients required intensive care unit admission, with 29% requiring mechanical ventilation. Respiratory symptoms typically manifest within 1 to 3 days posttrauma but can appear within 12 hours.[18] They may also arise suddenly after procedures related to fracture management, such as reduction, external/internal fixation, or manipulation of a tourniquet. Furthermore, their progression can be rapid or may significantly worsen in clinical scenarios where respiratory reserves are compromised, such as during anesthesia for surgery, necessitating close monitoring. These respiratory symptoms are relatively nonspecific and frequently occur in trauma patients, thus a differential diagnosis should be conducted for patients with clinical predisposition who exhibit such symptoms, considering the potential diagnosis of FES.

Neurological

Neurological impairments are nonspecific symptoms of FES. Although many symptoms are typically of cerebral origin, spinal cord ischemia can occur, and ocular symptoms such as retinal ischemia are also classified under neurological impairments. Symptoms of cerebral fat embolism often resemble those of diffuse encephalopathy and do not present with lateralization. However, there have been reported cases where spinal cord infarction, presenting initially as paraplegia, was a manifestation of FES.[19] Focal seizures resulting from FES frequently progress to generalized seizures and may even lead to status epilepticus.[20] Generally, symptoms can range from mild nonspecific manifestations such as anxiety and drowsiness in conscious patients to complete loss of consciousness in severe cases. Complete loss of consciousness has been reported as the first symptom of FES.[21] Rapid progression of loss of consciousness following a long bone fracture or related surgery should raise suspicions of FES. Butteriss et al.[22] reported that these symptoms are due to cerebral edema and encephalitis, attributable to the cytotoxic effect of free fatty acids that have crossed the blood-brain barrier and to inflammatory mediators activated during FES. In rare cases, fat droplets invading the subarachnoid space have triggered FES, and instances have been reported where ruptured dermoid cysts have caused neurological symptoms.[23] Although numerous alterations in the central nervous system are often reversible, irreversible fatal consequences, including brain death, have been reported.[24] Neurological symptoms usually accompany respiratory issues, providing a clinical clue that may suggest FES. However, there are rare cases where neurological symptoms appear without respiratory issues, making FES difficult to suspect. Thus, not considering FES as one of the differential diagnoses in trauma patients with neurological symptoms but no traumatic intracranial lesions is risky.

Cardiovascular

Hypotension is the most common cardiovascular manifestation of FES. It may occur alone or associated with tachycardia or arrhythmias. Echocardiography may reveal pulmonary arterial hypertension and a reduced in stroke volume. Large fat emboli can lead to rapid cardiovascular collapse, and in severe cases, it may result in cardiac arrest due to right heart failure leading to death. However, many symptoms are limited and transient. Pulmonary arterial hypertension may result from mechanical causes such as fat emboli obstructing the pulmonary vessels and biochemical changes that induce pulmonary vasoconstriction. Hypotension and tachycardia associated with FES are often subclinical but may exacerbate the shock state caused by injury to other organs, potentially worsening the clinical situation during the induction of anesthesia or in cases of surgery-related bleeding, delaying patient recovery. Conversely, cerebral fat embolism may induce paroxysmal sympathetic hyperactivity syndrome, temporarily causing arterial hypertension.[25] This condition is nearly always accompanied by tachycardia and may also present with tachypnea, diaphoresis, and hyperthermia—symptoms indicative of stimulated sympathetic tone. These symptoms may occur spontaneously or may be triggered by stimuli such as pain or airway suctioning, because of fat emboli causing elevated systemic catecholamine levels due to increased central catecholamine secretion.[26] Recognizing these clinical signs and understanding the clinical progression of FES are essential for treatment and may help reduce unnecessary testing.

Dermatological

A skin petechial rash is the most common clinical manifestation of FES, occurring in approximately one third of the cases. These nonpalpable petechiae typically appear on the subconjunctival, oral mucosa, neck, armpits, and chest areas

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and usually resolve within 24 hours. Although the rash resembles skin manifestations occurring in systemic inflammatory conditions such as disseminated intravascular coagulation or septicemia, it is distinctive because it appears primarily on the anterior chest. Tachakra[27] hypothesized that this phenomenon is due to fat emboli accumulating in the aortic arch and subsequently causing embolic events in nondependent skin areas. The pathophysiology of FES, including peripheral blood stasis, consumption of coagulation factors, reduction in platelet count, and damage to endothelial cells by free fatty acids, is recognized as a contributing factor to the onset of a petechial rash.[28]

Retinal

In FES, symptoms such as blurred vision, vision loss, and visual field defects can occur and are reported in approximately 50% of cases.[29] These symptoms, part of the ocular fat embolism syndrome, arise from retinal ischemic events caused by fat emboli. Subconjunctival or direct retinal petechial lesions are also observed, and jaundice may occur. More detailed ophthalmological examinations may reveal exudates or conjunctival edema. While these lesions generally resolve within a few weeks, they can permanently result in scotomas, known as Purtscher's retinopathy.[30]

Laboratory

Anemia without an identifiable cause is the most frequently reported abnormal finding in blood tests. Bulger et al.[4] observed anemia in 67% of FES patients. Such anemia rarely deteriorates to the extent that transfusion is necessary when no other causes are present. In addition, increases in thrombocytopenia and alveolar-arterial O_2 gradient have been reported in patients with long bone fractures without any clear cause.[4]

Pathophysiology

The pathophysiology of FES remains incompletely elucidated, but it is widely hypothesized in two ways: the mechanical and the biochemical hypothesis. Both hypotheses are supported by clinical evidence and animal studies, which suggest that they do not contradict each other, but rather the pathophysiological mechanisms described by each may concurrently contribute to the development of FES (Fig. 1).

Mechanical Theory

The mechanical theory, initially proposed by Gauss in 1924, attributes the origin of FES to trauma or surgical manipulation that disrupts fat-rich tissue within bone marrow and damages blood vessels. This disruption causes fat droplets to be drawn into lower-pressure, open-ended venous channels. The adipose emboli subsequently travel through the venous circulation and may occlude minor pulmonary arterioles, with diameters up to 20 μm, leading to ischemic necrosis.[31] In the pulmonary capillaries, the impacted fat emboli lead to a proinflammatory reaction, increase platelet adhesion, and contribute to fibrin production, culminating in thrombus formation. This process results in interstitial hemorrhage and alveolar decruitment, accompanied by secondary hypoxemic vasoconstriction. In addition, larger fat droplets can directly cause significant vascular occlusion, potentially leading to right heart failure and shock.

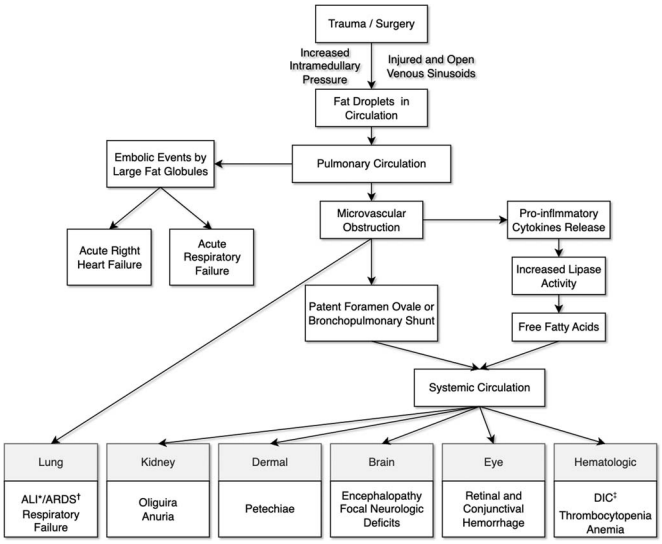

Figure 1. Pathophysiology of fat embolism syndrome. ALI, acute lung injury; DIC, disseminated intravascular coagulation.

Symptoms of cerebral fat embolism are caused by smaller fat particles (7–10 μm), which can bypass the lung's filtration system and travel to target organs, inducing FES symptoms.[32] Nevertheless, the mechanical theory does not entirely explain how larger fat emboli bypass the pulmonary circulation to enter the systemic circulation. The dissemination of fat emboli to extrapulmonary organs through a patent foramen ovale has been documented, although patent foramen ovales are present in only 25% to 30% of the population.[33,34] Nijsten et al.[35] noted that FES could occur in patients without patent foramen ovales or right-to-left cardiac shunts, as documented by transesophageal echocardiography. Findlay and DeMajo[36] postulated that, when right atrial pressure is sufficiently high, some fat globules might be forced from the lungs' capillary system into the pulmonary venous system. Others have proposed that fat emboli may gain entry into the systemic circulation via pulmonary-bronchial shunts.[37] Although the mechanical theory is appealing and supported by significant clinical and experimental evidence, Aoki et al.[38] argued that not all patients with large fat globules detected by echocardiography exhibit FES, suggesting that additional factors contribute to its pathogenesis and emphasized the need for further pathophysiological theories to elucidate its development.

Biochemical Theory

The biochemical theory does not deny the significant role of fat emboli generation and their dissemination following trauma in the manifestation of FES. Lehman and Moore[39] in 1927 identified that lipase, detected around fat emboli impacted in pulmonary vessels, catalyzed the conversion of adipose tissue into free fatty acids, which in turn causes local inflammatory responses such as endothelial edema and hemorrhage, constituting the main pathophysiology of pulmonary symptoms of FES. Elevated levels of proinflammatory cytokines, including tumor necrosis factor α, interleukin 1, and interleukin 6, are detected at these sites and contribute to the aggregation of blood lipids into large molecules, thereby inducing thrombosis.[40] Damage to pulmonary epithelial cells leads to interstitial edema, increased permeability, and surfactant deactivation, resulting in the collapse

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of alveoli. These local changes within the lungs fundamentally mirror the pathophysiology of ARDS, making it difficult to distinguish ARDS caused by other reasons from FES.[41] The increase in free fatty acids, which can occur in various clinical scenarios beyond long bone fractures, makes the biochemical theory useful in explaining FES that arises in nontraumatic conditions such as liver dysfunction, septicemia, and pancreatitis.[42]

DIAGNOSIS

There are no single laboratory tests or radiological examination that definitively diagnose FES. Fat embolism syndrome presents with nonspecific signs and symptoms affecting various organs, including the respiratory, neurological, and integumentary systems, making its diagnosis challenging. It is essential to be aware of clinical situations that can lead to FES, and upon the appearance of such symptoms, a diagnosis should be made by excluding other potential causes through an integration of biochemical tests and radiological assessments.

Diagnosis Criteria

In 1970, Gurd[18] first published the initial diagnostic criteria for FES based on an investigation including 100 individuals with long bone fractures. Those criteria were later modified by Wilson,[43] which became widely used. They proposed that the diagnosis of FES would be established upon the identification of at least two major clinical manifestations, or one major and four minor clinical manifestations simultaneously. Major clinical features included respiratory distress, neurological symptoms, and petechial rashes, while minor clinical features included evidence of fat droplets in urine or sputum specimens, kidney involvement, jaundice, ocular involvement, fever, tachycardia, unexplained changes in platelet and hematocrit levels, and fat macroglobulinemia. However, these diagnostic criteria lacked one of FES's characteristic respiratory clinical manifestations, namely, hypoxemia, leading Lindeque et al.[44] to propose revised criteria that included arterial blood gas analysis values. Schonfeld et al.[45] created a diagnostic system that assigned specific weights to clinical findings and used 5-point diagnostic cutoff values. Using this system, the reported incidence rate of FES was approximately 29%, which is higher compared with other comparable series. These three diagnostic criteria have all been used in clinical practice and are well-known because they do not require specialized test results (Table 1). However, they have the drawback of being very nonspecific, since most of the symptoms can also occur in other clinical traumatic scenarios, and these criteria have never been prospectively validated in a sufficiently large cohort, making their routine use in clinical practice not ideal.[1]

Laboratory Studies

Currently, no standalone laboratory assay is capable of diagnosing FES. Although thrombocytopenia and anemia are commonly observed alongside elevated levels of various inflammatory markers, these manifestations lack specificity for diagnostic purposes. Furthermore, associated findings such as hypocalcemia, increased serum lipase, and elevated levels of free fatty acids contribute to a reduction in the concentration of free albumin in the blood. In addition, while the presence of fat droplets in the bloodstream has been noted, this observation does not provide specific diagnostic utility for FES.

The diagnostic utility of measuring changes in certain inflammatory cytokines has been studied. Prakash et al.[46] reported that an increase in interleukin 6 approximately 12 hours after trauma in patients with femur and pelvic fractures was statistically associated with FES. Efforts to detect fat globules captured by macrophages in urine have been reported, but these methods have shown low sensitivity and specificity.[47] Studies have been conducted to use free fat globules or fat globules captured by macrophages in bronchoalveolar lavage specimens for diagnosing FES. Although fat globules were detected in up to 40% of

TABLE 1. Proposed Diagnostic Criteria of FES[43–45]

Gurd and Wilson*	Lindeque et al.**	Schonfeld et al.†
Major	PaO_2 < 60 mm Hg	Petechiae (5 points)
Respiratory insufficiency	$PaCO_2$ < 55 mm Hg or pH < 7.3	Alveolar infiltrates (4 points)
Cerebral involvement	Tachypnea >35/min	Hypoxemia (<70 mm Hg) (3 points)
Petechial rash	Increased work of breathing‡	Confusion (1 points)
Minor		Fever >38°C
Pyrexia		Heart rate >120/min
Tachycardia		Respiratory rate >30/min
Retinal changes		
Jaundice		
Renal insufficiency		
Laboratory		
Anemia		
Thrombocytopenia		
High erythrocyte sedimentation rate		
Fat macroglobulinemia		

*One major + 4 minor + fat microglobulinemia.
**Femur or tibia fracture + 1 feature.
†Five or more points.
‡Dyspnea, use of accessory muscles, tachycardia, and anxiety.

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the cases in the studies, this finding was not relevant, as it can also occur postsepticemia, hyperlipidemia, or following lipid emulsion therapy for other purposes.[1]

IMAGING STUDIES

Lung

At present, the most reliable method for diagnosing FES includes using radiological findings and clinical information. Typically, abnormalities on simple chest radiographs of FES cases with respiratory symptoms are observed in about 30% to 50% of cases, displaying bilateral, patchy, or ill-defined opacities in the lungs. However, these findings are also common in conditions such as pneumonia, pulmonary edema, and ARDS and typically lag behind clinical symptoms by about 12 to 24 hours.[48] High-resolution lung computed tomography scans can reveal more severe, well-demarcated ground glass opacities and interlobular thickening in both lungs, depending on the severity of symptoms, known as the "crazy paving pattern."[48] The occurrence of intraluminal filling defects, typically seen in pulmonary thromboembolism, is very rare.[49] A ventilation-perfusion scan may also detect perfusion defects, which may significantly aid in distinguishing thromboembolism from FES.

Brain

Conventional brain computed tomography scans frequently yield normal results in cases of FES or cerebral fat embolism. In more extreme cases, diffuse cerebral edema might be apparent. Occasionally, small hypodense changes or punctate hemorrhages may be seen around the periventricular white matter.[50] Presently, diffusion-weighted imaging (DWI) is the most sensitive diagnostic modality to identify cerebral fat embolism.[32,50] In DWI, fat embolism lesions display a characteristic "starfield pattern," which consists of small high-signal intensity spots scattered discontinuously against a dark background and appear darker in susceptibility-weighted sequences. Lesions are primarily found in the cerebellum, subcortical, periventricular, thalamus, basal ganglia, and deep white matter areas. Suzuki et al.[51] observed several patchy lesions at the watershed area of major vessels, suggesting that fat globules might be obstructing the capillaries (Fig. 2). Although these findings can also occur in other diseases, they may be helpful in diagnosing FES when considered in the clinical context of recent fractures that could cause FES, coupled with observed neurological symptoms. Localized, irreversible ischemic damage in these areas can show evidence of cytotoxic edema, appearing bright on DWI. This finding contrasts with diffuse axonal injury, which, while appearing similar, presents lesions at the junction between gray and white matter. Magnetic resonance imaging findings suspected to be caused by fat embolism can change in size and signal characteristics over time. Takahashi et al.[52] observed that high-signal intensity findings on Transverse Relaxation Time 2 (T2) Magnetic Resonance Imaging (MRI) fused and expanded over time, mostly decreasing within 2 weeks and attempted to classify the severity of cerebral fat embolism into four categories based on these changes. Their study reported favorable outcomes in cases where lesions in the deep white matter had completely resolved, while the most unfavorable outcomes were seen in cases where lesions remained even after 2 months. Forteza et al.[53] documented in their investigation of individuals with femoral fractures that transcranial Doppler could predict the onset of neurological symptoms and noted a higher occurrence of ultrasound findings suggestive of cerebral microembolism, especially in patients with cardiac shunts. Others have also reported that monitoring microemboli with transcranial Doppler during or after surgery on the legs and pelvis can be somewhat useful.[54]

MANAGEMENT

There is no definitive treatment for FES once it has occurred. The most appropriate management strategy includes prevention and perioperative care, with supportive care serving as the main strategy after its onset. A critical aspect lies in prioritizing prompt resuscitation and stabilization in the early stages to attenuate the physiological stress response and effectively address hypovolemia (Fig. 3).

Early Fixation

The most emphasized preventive measure for FES in the management of trauma patients is early fixation of the fracture site. Numerous studies have reported positive effects of early stabilization of fractures in preventing FES.[55–57] Robinson[58] compiled studies conducted until 1997 and performed a meta-analysis reporting that early fixation of fractures can achieve approximately 70% reduction in pulmonary complications. Pulmonary complications and extended hospital stay occur when

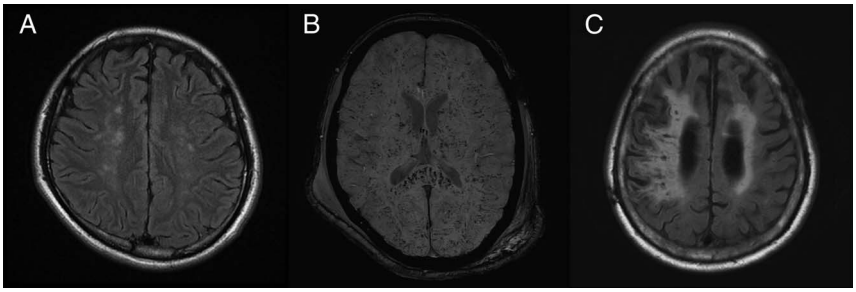

Figure 2. Magnetic resonance image characteristics of cerebral fat embolism syndrome. (*A*) Typical small multifocal lesions, which can be identified relatively early on DWI, are referred to as a starfield pattern. (*B*) Multiple microhemorrhages in the white matter on SWI, are referred as a walnut kernel pattern (see multiple small black dots distributed throughout the white matter). (*C*) On Transverse Relaxation Time 2-Fluid Attenuated Inversion Recovery images, lesions cluster together and become larger with indistinct margins several weeks to months after the initial event. SWI, susceptibility weighted image.

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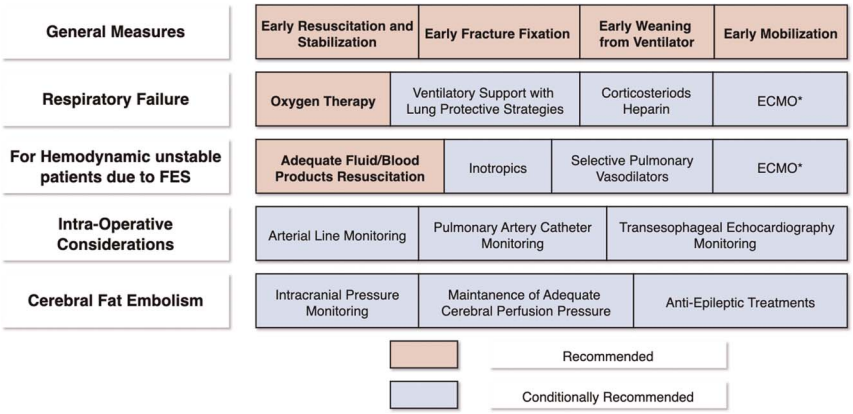

Figure 3. Management strategies to patients at risk on sustaining fat embolism syndrome. ECMO, extracorporeal membrane oxygenation.

fixation is delayed for over 24 hours in polytrauma patients.[59] However, if operative fixation is performed in patients who have already manifested symptoms of FES, there is a risk of exacerbating FES symptoms during surgery.[60] Therefore, some authors postulate that it is essential to perform damage-control fixation promptly in polytrauma patients and then carefully decide on the timing of definitive fixation based on the clinical scenario in patients showing signs of FES or in those considered high risk for developing FES.[58]

Orthopedic Procedures

External fixation or plate fixation is considered less detrimental to the lungs compared with intramedullary fixation. The pressure exerted by nail insertion after reaming is similar to that of an unreamed nail. However, the incidence of fat embolism is reduced with unreamed nails. The choice of reamer also influences the risk, with blunt reamers producing higher pressures compared with sharp ones,[61] and hollow nails resulting in lower pressures than solid ones. In addition, repeatedly moving the reamer in and out can induce high pressure peaks.[62] Ultrasonic reamers have been shown to significantly increase emboli during revision arthroplasty.[63] Dalgorf et al.[64] suggested a procedure that connects ventilation to reduce intramedullary pressure during surgery, but it has not been widely adopted. Others proposed using a tourniquet or performing bone marrow lavage before inserting intramedullary devices, although these techniques have limited effectiveness and are not yet widely used.[65]

Pharmacologic Strategies

To date, drugs such as *N*-acetylcysteine, steroids, aspirin, dextran, hyperosmolar saline, and sildenafil have been evaluated for their potential in preventing FES in animal models or small-scale patient studies. However, no medications have been definitively recommended as mainstream treatment of FES.[66–68]

Several studies have highlighted the potential positive effects of corticosteroids in preventing respiratory failure due to FES. These effects may include stabilizing the pulmonary endovascular membrane, thereby reducing endothelial leakage that leads to interstitial edema, suppressing inflammatory reactions, maintaining the stability of complements activation, and inhibiting platelet aggregation. Studies using doses of methylprednisolone ranging from 9 mg/kg to 90 mg/kg (administered in fractionated doses) have demonstrated significant better outcomes, including a 10-fold decrease in the incidence of FES in one series.[44,45,67] Bederman et al.[69] documented, in a meta-analysis of 104 studies, that corticosteroids could prevent FES and hypoxia without increasing the infection risk, although they observed no impact on mortality. A 2012 review also reported favorable outcomes with significantly fewer steroid-treated patients developing FES compared with controls among 483 participants.[70] However, interpreting these results is challenging because of the variability in sample sizes, steroid dosing, and treatment durations. Considering the rarity of FES, the potential adverse effects associated with corticosteroid administration, and the absence of robust evidence, the routine utilization of prophylactic costicosteroid is not advised. Additional research is needed to determine the optimal timing for the administration of corticosteroid therapy and to comprehensively understand its effects.

Heparin has been suggested as a treatment for FES by enhancing lipase activity to clear lipemic serum; however, its effectiveness in FES is debated.[71] If increased free fatty acids are critical in FES development, then stimulating lipase might be a dangerous treatment. Moreover, the use of heparin, which can increase bleeding, is very limited in treating trauma patients. To prevent free fatty acids mobilization, ensuring an adequate glucose supply has been used as a preventive approach.[72]

Aspirin has been recommended to prevent gas exchange disturbances and to inhibit thromboxane production in animal FE models.[73] Dextran is avoided because of its deleterious impact on renal function and coagulation. Heparin, aspirin, and dextran all decrease platelet adhesiveness, consequently mitigating the formation of microaggregates.[74] Administering high-dose statins after cerebral fat embolism might improve patient outcomes,[75] but further research is needed to confirm the effectiveness of statins in the management of cerebral fat embolism. Recent experimental studies have explored modifying the renin-angiotensin pathway to counteract FES. Angiotensin II, known for its vasoconstrictive, proinflammatory, and profibrotic effects, may play a role in FES pathogenesis by enhancing local renin release when fat is taken up by lung macrophages, leading to increased levels of angiotensin I and II.[76] Depending on the extent of hemodynamic deterioration, limited fluid resuscitation and the use of inotropic drugs may be attempted. If pulmonary

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hypertension is severe, the restricted use of pulmonary vasodilators or nitric oxide as rescue therapy may be considered.

Critical Care

Respiratory and cardiovascular monitoring during surgery is beneficial for all patients at risk of FES, particularly those with femur fractures. Consistent utilization of pulse oximetry facilitates the early identification of hypoxemia, enabling prompt intervention. In patients without sufficient physiological reserve, an arterial pressure line and invasive monitoring measures is advisable. The utility of monitoring pulmonary artery pressure through the insertion of a pulmonary artery catheter is controversial. Although pulmonary artery pressure tends to increase with FES, the degree is inconsistent, and the absence of increased pulmonary pressure does not rule out fat embolism. However, if a rapid increase in pressure occurs in the presence of clinical signs, it can increase the suspicion of the onset and exacerbation of FES. Transesophageal echocardiography is the most useful tool for detecting systemic dissemination of fat emboli during surgery. Fat globules can appear as multiple hyperechoic material in the right atrium, aiding the diagnosis along with clinical symptoms and helping exclude other causes when hemodynamic deterioration occurs rapidly during surgery. There is no clear recommendation to screen for patent foramen ovale before lower extremity orthopedic surgeries. The management of respiratory symptoms resulting from FES postsurgery closely aligns with the approaches for acute lung injury/ARDS. Key principles involve early mobilization, when possible, spontaneous breathing and coughing, implementing positive end-expiratory pressure, and reducing sedation and the administration of neuromuscular blocking agents.[77] If the patient responds adequately, has low risk of airway obstruction, and exhibits mild to moderate hypoxemia, management with high flow oxygen, continuous positive airway pressure, other noninvasive respiratory support modalities, and oxygen supply methods are indicated. In contrast, severe hypoxemia and decreased consciousness require intubation and mechanical ventilation. In such cases, appropriate sedation and analgesia are essential, although neuromuscular blockers are not always necessary.[78] Acute right heart failure may occur because of extensive pulmonary embolism. Treatment should focus on maintaining adequate right heart filling pressure and alleviating pulmonary hypertension to reduce right ventricular afterload. Ensuring sufficient preload via isotonic fluid resuscitation and using selective pulmonary vasodilators to prevent systemic arterial hypertension or worsening hypoxemia resulting from ventilation/perfusion imbalance are paramount. Agents such as sildenafil, prostacyclin, and nitric oxide may prove efficacious in reducing pulmonary vascular resistance. Maintaining systolic arterial pressure near right ventricular systolic pressure is recommended to ensure adequate perfusion of the right ventricle. If adequate circulation cannot be achieved, support by means of extracorporeal membrane oxygenation may be necessary.

The primary treatment for cerebral dysfunction following cerebral fat embolism is supportive care. Meticulous monitoring of intracranial pressure and maintenance of adequate cerebral perfusion pressure are critically important.[79] Although clinical diagnosis remains the preferred method for identifying the cerebral component of FES, MRI has proven beneficial for evaluating the extent of cerebral fat embolism and predicting long-term prognosis in the absence of traumatic brain injury. A summary of potential treatment strategies is displayed in Figure 3.

Prognosis

While 10% to 44% of individuals with FES necessitate mechanical ventilatory support, pulmonary dysfunction usually resolves within 3 to 7 days.[4,80] Currently, there is a lack of long-term follow-up studies specifically examining the outcomes of patients with FES. The estimated average mortality rate, mostly derived from clinical cases and retrospective studies, is approximately 10%.[4,5] Although severe clinical symptoms are associated with a higher mortality rate,[81] reports indicate that 90.5% of patients who develop focal neurologic deficits or seizures ultimately experience favorable outcomes.[32]

AUTHORSHIP

J.K. and R.C. planned the design of the review and participated in the literature review, writing, and editing of the manuscript.

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DISCLOSURE

Conflicts of Interest: Author Disclosure forms have been supplied and are provided as Supplemental Digital Content (http://links.lww.com/TA/D932).

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